REMARKS

Following entry of the foregoing amendments, claims 34, 37, 38, 49, 53 to 62, 72, 74 to 78, 94 to 96, and 104 will be pending. Claims 34 and 94 have been amended, and claims 4, 5, 50, and 63 have been canceled, herein, without prejudice. No new claims have been added. Support for the amendments is found throughout the specification as originally filed. For example, support for the amendments to claim 34 is found in paragraphs 27 and 89. The amendments thus do not introduce new matter into the application.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Alleged Obviousness

Claims 34, 37, 38, 49, 50, 53 to 63, 72, 74 to 78, 94 to 96, and 104 were rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Elbashir *et al.*, *EMBO Journal*, 2001, 20, 6877-6888 ("Elbashir"); published U.S. patent application number U.S. 2003/0143732 ("Fosnaugh"); and published U.S. patent application number U.S. 2003/0206887 ("Morrissey") in view of the combined teachings of U.S. patent number 6,262,036 ("Arnold"); published U.S. patent application number U.S. 2005/0142535 ("Damha"); and U.S. patent number 6,133,246 ("McKay"). Applicants respectfully request reconsideration and withdrawal of the rejection because the presently claimed compositions would not have been obvious to one of ordinary skill in the art at the time of the invention.

The claims as amended recite compositions that comprise two chemically synthesized oligomeric compounds in which at least one of the oligomeric compounds comprises nucleosides having 2'-F substituent groups that alternate with β-D-deoxyribonucleosides. Elbashir, Fosnaugh, Morrissey, Arnold, Damha, and McKay fail to teach or suggest such oligomeric compounds having this particular pattern of chemical modifications. As discussed in the previous response, the references merely provide generalized teachings regarding chemical modification of RNA or describe oligomeric compounds that have patterns of chemical modifications that differ significantly from the pattern claimed.

As discussed previously, Fosnaugh merely provides generalized teachings regarding chemical modification of RNA. The application provides a broad list of possible chemical

modifications for oligomeric compounds and states that such modifications can be incorporated into siRNA molecules. This generalized teaching cannot render obvious all possible motifs, such as those presently claimed.

Elbashir describes siRNA duplexes in which each nucleoside of one or both strands is either 2'-OMe or 2'-deoxy. As the Examiner notes, "substitution of one or both siRNA strands by 2'-deoxy or 2'-O-methyl oligonucleotides abolished RNAi." Office Action at page 7 (quoting Elbashir abstract). That conclusion teaches away from the present invention, in which each nucleoside of the one or both strands is either 2'-F or 2'-deoxy. The Examiner now relies on pages 6881-6882, discussing use of 2'-deoxynucleosides in non-pairing overhangs. Noting that 2'-deoxynucleoside overhangs are tolerated, the Examiner mistakenly concludes that Elbashir teaches that "only the complete substitution of the strand with these modifications leads to abolished activity." Office Action at page 9 (emphasis original). That is not correct. Elbashir teaches only that (1) complete substitution abolishes activity and that (2) 2'-deoxynucleosides in the non-pairing overhangs are tolerated. Elbashir does not teach that "only the complete substitution" abolishes activity. Beyond the tolerance of 2'-deoxy overhangs and total loss of activity by certain full modification, Elbashir provides no guidance as to which modifications at what positions may be tolerated. Elbashir does not provide any guidance as to which other possible substitution patterns (untested by Elbashir) also abolish activity. Remarkably, the narrow teaching of Elbashir actually teaches away from the present invention. As noted by the Examiner, Elbashir warns against fully modified strands. And the present claims in fact recite fully modified strands - duplexes in which each nucleoside of one or both strands is modified from RNA (either 2'-F or 2'-deoxy). Elbashir teaches very little about what substitutions and motifs are tolerated. What little it does teach actually teaches away from the present invention.

Morrissey describes chemically-modified siRNA molecules that target hepatitis B virus. The application provides a general description of various possible 2' modifications and states that such modifications can be introduced into the described siRNA molecules. As previously noted, the application teaches that the 2' modifications can be placed at either the 3' or 5' ends of the siRNA molecules or at internal pyrimidine-containing nucleotides. The present claims do not recite modifications limited to the ends. Further, Morrissey describes siRNA molecules in which each pyrimidine has the same modification. When such modified pyrimidines are incorporated

into a siRNA, the pattern of modification will depend on the base sequence rather than on a pre-determined modification motif. This approach implies that the pattern of modifications is not important and differs fundamentally from the present invention.

Individually or in combination, Fosnaugh, Elbashir, and Morrisey fail to teach the elements of the present claims. The remaining references are directed to RNase H based antisense technology and the Examiner's reliance on those references is inapt.

Arnold, Damha, and McKay describe certain oligonucleotides for use in RNase H based antisense. One of skill in the art at the time of filing would not look to RNase literature in designing siRNA oligomers. Indeed, the Examiner noted that "[n]o assumptions existed in the art at the time of the instant invention that the same configurations that were optimal for RNase H activity (e.g., as described in Damha) are applicable to siRNA." Office Action at page 5. Further, even if one did look to that RNase H literature, one would be led to motifs such as gapmers which do not work in siRNA and are not claimed by the present invention. Accordingly, these references are at least irrelevant and at most teach away from the present invention.

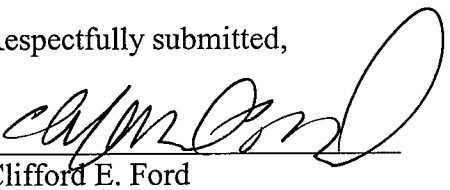
For at least the above reasons, the claims are non-obvious. Accordingly, Applicants respectfully request the rejections based on 35 U.S.C. § 103 be withdrawn.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 50-0252 and please credit any excess fees to such deposit account.

Respectfully submitted,



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